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Management of nystagmus in children: a review of the literature and current practice in UK specialist services

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36 **Abstract**

37

38 Nystagmus is an eye movement disorder characterised by abnormal, involuntary
 39 rhythmic oscillations of one or both eyes, initiated by a slow phase. It is not
 40 uncommon in the UK and regularly seen in paediatric ophthalmology and adult
 41 general/strabismus clinics. In some cases, it occurs in isolation, and in others, it occurs
 42 as part of a multisystem disorder, severe visual impairment or neurological disorder.
 43 Similarly, in some cases, visual acuity can be normal and in others can be severely
 44 degraded. Furthermore, the impact on vision goes well beyond static acuity alone,
 45 is rarely measured and may vary on a minute-to-minute, day-to-day or month-to-
 46 month basis. For these reasons, management of children with nystagmus in the UK is
 47 varied, and patients report hugely different experiences and investigations. In this
 48 review, we hope to shine a light on the current management of children with
 49 nystagmus across five specialist centres in the UK in order to present, for the first time,
 50 a consensus on investigation and clinical management.

51

52

53

54 **Introduction and demographics**

55

56 The estimated prevalence of nystagmus in the UK is 24 per 10 000(1). It can be
 57 broadly grouped into Infantile Nystagmus Syndrome (INS) and acquired nystagmus.
 58 The onset of INS is usually within the first 6 months of life (average age =
 59 1.9 months)(2). INS can be idiopathic, associated with albinism, retinal diseases such
 60 as achromatopsia, congenital stationary night blindness (CSNB) or early onset retinal
 61 degenerations, low vision in infancy, and a variety of other syndromes and
 62 developmental diseases (for an exhaustive list, see Leigh and Zee [2006])(3). The
 63 most common forms of INS are idiopathic INS and INS associated with albinism or
 64 retinal diseases. The most common form of non-INS nystagmus in childhood, is
 65 Fusional Maldevelopment Nystagmus Syndrome (FMNS, previously Manifest Latent
 66 Nystagmus MIN).

67

68 Children with nystagmus can be severely visually impaired or can have almost
 69 normal visual acuity (VA), depending on the underlying disease. However, VA is not
 70 a global measure of visual function and Nystagmus of any type can be associated with
 71 significant visual loss(4) beyond that of acuity alone, and accordingly, both
 72 nystagmus and albinism are cited as key priorities in the area of Childhood-Onset
 73 Disorders, as determined by the Sight Loss and Vision Priority Setting Partnership in
 74 2013.

75

76 Despite much research into nystagmus over many years, there are still many
 77 unanswered questions about diagnosis, treatment and broad management.
 78 Consequently, many clinicians are less comfortable managing children with
 79 nystagmus than other conditions and management varies widely. In this review, we

80 seek to clarify the current state-of-play regarding diagnosis, management,
 81 treatment options and the use of various investigations in managing this complex
 82 group of children.

83

84 **Basic clinical assessment**

85

86 *Patient history & examination*

87

88 When assessing the infant/child with nystagmus, although INS (with/without
 89 associated ocular disorders) is more common, it must be borne in mind that some
 90 infants and young children will have 'acquired' nystagmus with an underlying
 91 neurological cause. Indeed, some older children and/or adults will have previously
 92 undiagnosed INS or nystagmus associated with early lack of fusion (FMNS) or, less
 93 commonly, nystagmus secondary to severe acquired visual loss. History and clinical
 94 examination are both important in tailoring the management pathway to allow
 95 appropriate investigations and/or treatment. Since INS is associated with a wide
 96 range of underlying disorders, the presence of nystagmus in an infant/child should
 97 stimulate a comprehensive search for a cause. Table 1 summarises some of the
 98 important questions to be included in a thorough history.

99

100 The clinical examination begins before the child enters the room, particularly
 101 observing for signs of: photophobia, eye rubbing for retinal stimulation, head
 102 postures (variable/alternating/consistent) and/or head shaking (both often, but not
 103 always, after 1 year of age), skin/hair tone particularly in relation to other family
 104 members present, as well as signs of associated systemic and neurological features.

105 The examination can then be split into two parts: eye movements and ocular (+/-
 106 systemic) examination.

107

108 *Ocular & systemic examination*

109

110 An ocular examination should be performed with the best age-appropriate
 111 equipment available, specifically looking for ocular signs commonly associated with
 112 nystagmus, which may include:

113

114 **Cornea** – size (e.g. microcornea associated with coloboma, or buphthalmic eye
 115 associated with glaucoma), epitheliopathy (e.g. associated with *PAX6* gene
 116 disorders)

117 **Anterior chamber** – structure (e.g. anterior segment dysgenesis)

118 **Iris:** Iris structure (e.g. aniridia, coloboma), iris transillumination (e.g. albinism or some
 119 *PAX6* related disorders)

120 **Lens** – cataract, aphakia (congenital/acquired), intraocular lens implant following
 121 previous surgery

122 **Vitreous** – clarity (e.g. vitreous haemorrhage)

123 **Retina and Optic Nerve** – structure e.g. coloboma, disc anomalies (e.g.
 124 papilloedema, hypoplasia, coloboma or small cup seen in albinism), retinal
 125 hypo/hyperpigmentation and or pigment, foveal structure (e.g. hypoplasia, atrophy
 126 from congenital infection).

127

128 Ocular disorders commonly associated with INS are summarized in Table 2.

129

130 Where there is any concern that there is an associated systemic or neurological
 131 disorder based on either the eye examination or the overall assessment of the child,
 132 the infant/child should also be reviewed by a paediatrician or paediatric
 133 neurologist.

134

135 *Red flag signs*

136

137 Red flag signs are features in the history and examination which should alert the
 138 clinician to acquired pathology that requires further systemic investigations such as
 139 neuroimaging.

140

Red Flag Signs

- Latent onset nystagmus (in the absence of signs in keeping with an ocular disorder)
- Constant oscillopsia in older children
- Dysconjugate/gaze evoked/see-saw/convergence-retraction nystagmus
- Horizontal nystagmus becoming vertical in vertical gaze
- Vertical or torsional nystagmus (in the absence of retinal pathology (e.g. achromatopsia))
- Any associated neurological signs and/or a systemically unwell child

141

142 *Family history*

143

144 Taking an accurate family history is an important part of the initial evaluation for all
 145 children with nystagmus. If a clear family history of nystagmus is noted, identifying
 146 the structure of the pedigree (family tree), in addition to information about the

clinical characteristics of those affected, is key. Sometimes it will become apparent that the nystagmus in older relatives seems to be isolated and, in others, is associated with other visual disorders (such as retinal dystrophies or aniridia) or systemic disorders (such as ataxia in the case of spino-cerebellar ataxia syndromes). Asking the degree of visual disability and treatment history for those affected can help to differentiate these groups of disorders. In other cases, the history may include apparently non-ocular disorders (such as relatives with strikingly pale skin and hair in contrast to the family context in albinism disorders) or ocular disorders without nystagmus (such as unexplained low vision from a young age in older relatives or night blindness). It is therefore important to ask about any medical disorders in relatives, whether they seem to be related to nystagmus or not, and in all cases to draw a family pedigree in order to narrow the search for potential hereditary causes (and reduce the number of investigations needed in many cases). In many cases, especially where full cooperation is difficult in a young child, examining parents can yield diagnostic information (such as iris transillumination in parents as a clue to albinism as an underlying cause). Figure 1 shows how to draw a pedigree diagram and includes a key to remind clinicians how such diagrams are constructed.

CLINICAL TIP: When drawing a pedigree diagram, start with the proband (the presenting patient) and work horizontally before vertically where possible. Also include names and dates of birth when available (and according to local data protection policy) and older siblings to the left and younger siblings to the right.

Figure 1.

172 *Orthoptic examination*

173

174 Orthoptic examination of all children presenting with nystagmus is essential, not only
 175 for the comprehensive assessment of visual function and VA throughout the critical
 176 period of visual development, but also for investigation of ocular alignment and
 177 binocular vision(5). This is required due to increased prevalence of strabismus in the
 178 presence of childhood nystagmus, reported as between 16 and 52%(6, 7). Children
 179 with idiopathic INS are less likely to develop strabismus, whereas those with
 180 congenital retinal dystrophies or albinism are at intermediate risk, and those with
 181 bilateral optic nerve hypoplasia are at particularly high risk(6).

182

183 Clinical recommendations for the orthoptic assessment, additional to those
 184 discussed in other sections of this paper, are summarised in Table 3; the specific
 185 investigation in each case will depend on the age and co-operation of the patient.
 186 Additional clinical investigations may be required depending on findings and clinical
 187 judgement.

188

189 Giving time and relaxing the child as much as possible so that they are comfortable
 190 during the orthoptic assessment may give the best performance and improve the
 191 responses recorded, as both anecdotal reports from patients and experimental
 192 studies have reported that the nystagmus intensity increases with increased effort to
 193 fixate and decreases when relaxed (8, 9).

194

195 In the presence of nystagmus, the cover test will be more difficult to perform as small
 196 movements to take up fixation can be impossible to distinguish. Observation for
 197 asymmetrical corneal reflections may therefore be relied upon. Caution should be

taken as a significant association has been found between a positive angle kappa and clinical signs of albinism in patients with INS(10).

CLINICAL TIP: The involuntary head nodding often seen in INS can be distinguished from rhythmic head movement due to a more sinister cause; if the child can voluntarily stop the head movement when asked, it is caused by the nystagmus.

Nystagmus examination

A simple, methodical clinical assessment of a child's nystagmus can provide key information in order to direct further investigations. It can sometimes identify the type of nystagmus, but it can also rule out, or at least reduce the likelihood of, some nystagmus aetiologies. Even if the nystagmus type cannot be identified, it is important to document its features. There are different diagrammatic schemes for describing the nystagmus in the medical notes, but consistency is important. Using words, whilst verbose, does avoid confusion.

The initial and crucial task is to look for nystagmus in all gaze directions, not just primary position (usually the nine cardinal points). There may be nystagmus in far eccentric gaze, which can be easily overlooked in an uncooperative child, so perseverance is required. The axis of oscillation, whether it is horizontal, vertical, torsional, circumrotatory (i.e. circular or elliptical), or a mixture, should be noted at each cardinal point. Does the nystagmus appear similar in each eye (i.e. conjugate), or is there an asymmetry? If the nystagmus appears jerky, document the direction of the fast phase, otherwise note that it appears pendular. Note the frequency (how fast) and amplitude (how big).

224

225 It is also important to examine the nystagmus during monocular viewing to look for
 226 FMNS, which is relatively common either as the sole nystagmus or in conjunction with
 227 other types of nystagmus (usually INS). In sole FMNS, the nystagmus is conjugate,
 228 horizontal, and in primary position, beats in the direction of the viewing eye. That is,
 229 the nystagmus reverses with alternate occlusion. The nystagmus also intensifies with
 230 increased abduction of the viewing eye and dampens (sometimes completely) in
 231 full adduction. Thus, FMNS is usually best identified by alternating occlusion with the
 232 eyes in far lateral gaze, as this will bring out the biggest change in intensity. Patching
 233 may sometimes be preferable to an occluder in the young uncooperative patient.

234

235 Typically, INS is horizontal and remains so in elevation and depression. The nystagmus
 236 often has a null region (a direction of gaze in which the nystagmus dampens) and
 237 increases in intensity, becoming jerkier farther from the null.

238

239 Gaze evoked nystagmus is the most common acquired nystagmus. It is usually
 240 caused by cerebellar lesions/malformations or drug toxicities (esp. anticonvulsants).

241 The nystagmus is evoked on lateral gaze but absent in primary position. It beats in
 242 the direction of gaze, similar to FMNS but is unaffected by monocular occlusion.

243 There may (or may not) be downbeat nystagmus in lateral gaze or depression. In
 244 elevation, there may (or may not) be unsteady gaze or upbeat nystagmus.

245 Horizontal smooth pursuit is almost always quite saccadic, which is one way to
 246 differentiate it from endpoint nystagmus.

247

248 If the nystagmus is downbeat, upbeat or asymmetric, then a neurological cause
 249 should be considered, although INS cannot be excluded. Periodic Alternating

Nystagmus (PAN) describes a horizontal jerk nystagmus that reverses direction every few minutes. PAN can occur as an acquired neurological nystagmus or as an aspect of INS (often raising suspicion of albinism as the underlying aetiology). To test for PAN, the nystagmus should be examined for a reversal in direction for at least 5 minutes. It is important to keep the gaze in primary position, otherwise a spurious reversal could occur due to a gaze evoked null shift. Such prolonged observations can be difficult for young or non-compliant patients. If the nystagmus beat direction (or AHP) is different than indicated in previous notes or reports by carers, then PAN should be suspected. When associated with INS, PAN has no sinister implications but may be a contraindication for standard AHP surgery as it implies spontaneous null shifting.

CLINICAL TIP: For a more detailed, practical description of how to examine nystagmus and other supranuclear eye movements in children (and interpret findings), see: ‘Supranuclear eye movements and nystagmus in children: A review of the literature and guide to clinical examination, interpretation of findings and age-appropriate norms. Eye. 2019;33(2):261-73’ (11)

Specialised clinical assessment

Optical Coherence Tomography (OCT) in INS

OCT imaging has been established as a tool that can streamline diagnosis of the aetiology of INS.(12-32) For infants and young children who cannot cooperate with standard table-top OCTs, a hand-held spectral domain OCT imaging (HH-SDOCT) device can be used, which has been shown to be reliable in the presence of

nystagmus(33). By identifying the presence or absence of typical or atypical foveal hypoplasia (continuation of the normally absent inner retinal layers (IRLs) across the fovea) and the presence of other abnormal morphological features, it is possible to divide INS into four diagnostic categories: (1) typical foveal hypoplasia; (2) atypical foveal hypoplasia; (3) abnormal foveal morphology and (4) normal foveal morphology (Figure 2)(32). In this way, conditions such as albinism and *PAX6* mutations, which are usually associated with typical foveal hypoplasia (Figure 3A), can be distinguished from other conditions such as achromatopsia, which is characterised by atypical foveal hypoplasia (Figure 3B), or retinal dystrophies, which are typically associated with abnormal foveal morphology (Figure 3D). Furthermore, the severity of foveal hypoplasia can be graded (Figure 4), and this can potentially be used as a visual prognostic indicator.(34)

Figure 2

Figure 3

Figure 4

CLINICAL TIP: There are frequently movement artefacts in macular OCTs from patients with INS. When attempting to diagnose foveal hypoplasia, obtain a macular volume scan, ensuring that (a) the optic nerve is visible as a landmark and (b) there is a minimum of five uninterrupted Bscans (i.e. without refixations or blinks on either side of the central foveal Bscan).

Eye movement recordings in INS

301

302 Eye movement recording (EMR), if available, provides a means for objectively
 303 visualising the details of oculomotor phenomena that are not visible to the naked
 304 eye or occur transiently. EMR can also provide a permanent quantitative record for
 305 longitudinal comparisons to monitor disease progression or remission. EMR is
 306 particularly valuable for patients with oscillatory eye movements as it can reveal the
 307 underlying nystagmus waveform that distinguishes various types of nystagmus and
 308 saccadic oscillations. EMR recording can also detect abnormal smooth pursuit,
 309 saccades, OKN, and vestibular responses depending on the type of equipment at
 310 hand(35).

311

312 Modern eye trackers are mostly video-based and provide non-intrusive accurate
 313 recordings with high resolution for horizontal and vertical eye movements. Hence,
 314 they are capable of providing objective evidence for the presence and type of
 315 nystagmus, but also for the absence of nystagmus. Note that the majority of EMR
 316 systems do not record torsional eye movements; for this, highly specialised
 317 equipment is needed.

318

319 In a busy clinical setting, it is usually not possible to perform a standardised battery of
 320 eye movement recordings with each patient. Instead, and where available, eye
 321 movement recordings can help address outstanding clinical questions where other
 322 examination is equivocal. For example an accelerating slow-phase is virtually
 323 pathognomonic of INS, regardless of age and any underlying sensory defect(36).

324

325 Eye oscillations can occur intermittently, either as a post-saccadic phenomenon, or
 326 as a burst of oscillations with no apparent predisposing factor. The differential

diagnosis for these phenomena is wide including paroxysmal/epileptic nystagmus, organic ocular flutter, opsoclonus, psychogenic flutter, square wave jerks, and saccadic dysmetria. The intermittent nature can lead to difficulty in the identification, but are nearly always resolved by EMR. EMR can also provide useful information about other eye movement abnormalities, whether or not nystagmus is also present. For example, saccadic disorders are notoriously difficult to visualise clinically and various abnormalities such as disorders of speed, accuracy and triggering ability can be missed. Furthermore, approximately 1 in 20 people can voluntarily induce a high frequency, low amplitude ocular oscillation⁽³⁷⁾ called *psychogenic flutter*, sometimes incorrectly referred to as psychogenic/voluntary nystagmus. This phenomenon is not a form of nystagmus, as it consists of back-to-back saccades with no slow phase. It is not an uncommon reason for presentation to the paediatric eye clinic and must be differentiated from nystagmus or opsoclonus/ocular flutter which requires more extensive investigations.

If available, EMR can also be useful for surgical planning and monitoring results, e.g. through documentation of the presence or absence of PAN and/or the null zone position and pre and post-surgery waveforms. See Figure 5 for some clinical examples illustrating when EMR can be particularly useful in dictating subsequent investigation and management for children referred with nystagmus.

Figure 5

349

350 *Electrodiagnostics*

351 Visualelectrodiagnostics are tests that assess the function of the afferent visual
 352 pathway from retina to cortex. Retinal function is assessed using the
 353 electroretinogram (ERG) and the postretinal pathway using visually evoked potentials
 354 (VEP). Paediatric ERGs and VEPs are non-invasive, objective tests that do not require
 355 any anaesthesia, sedation or mydriasis. The tests are relatively quick to perform (30-
 356 40 minutes) with immediate access to results and are performed according to a
 357 modified, combined paediatric protocol(38). Adults with nystagmus should be
 358 investigated using the standards and recommendations of the International Society
 359 for Clinical Electrophysiology of Vision (ISCEV)(39).

360 A common cause for nystagmus in children is retinal dystrophy, and in many cases,
 361 a fleeting posterior segment examination is normal. These patients need ERGs and
 362 VEPs to assess retinal integrity and isolate cone and rod function: severe retinal
 363 dystrophy such as Leber's amaurosis, results in all ERGs being attenuated whereas, in
 364 achromatopsia, cone-mediated ERGs are attenuated but rod ERGs are normal.
 365 Alteration in the ERG waveform that results in a negative configuration (better
 366 preserved ERG 'a' wave than 'b' wave) is commonly seen in an X-linked CSNB and
 367 X-linked retinoschisis. Pigmentary retinopathies can also be associated with a
 368 number of systemic and neurometabolic conditions that may present with
 369 nystagmus: ERGs are degraded with rod responses often more severely affected
 370 initially with later involvement of the cones.

371 The concurrent recording of pattern VEPs determines the extent of macula
 372 involvement and provides an estimate of the level of vision. A patient could have
 373 extinguished flash ERGs but preserved pattern VEPs, indicating retinal dysfunction

374 primarily involving the extra-macular areas, whereas pattern VEPs are degraded in
 375 patients with cone dysfunction. VEPs should be recorded to a range of different size
 376 patterns: black and white checkerboard pattern that is alternating (pattern reversal)
 377 or appearing and disappearing (onset/offset VEPs). Patients with nystagmus have
 378 degraded pattern VEPs corresponding to their decreased vision. However, if ERGs
 379 are normal but VEPs are degraded to all pattern sizes, then a post-retinal problem
 380 needs to be excluded. Neurological conditions such as optic nerve hypoplasia,
 381 glioma, craniopharyngioma and achiasmia may present with nystagmus, and the
 382 VEPs in these patients can be abnormal not only in waveform, but also in distribution
 383 across the occiput. Midline and lateral scalp electrodes are used to enable the
 384 recording of the contributions of each occipital hemisphere to the VEP. If the
 385 occipital distribution shows an asymmetry that is similar for the two eyes (uncrossed
 386 asymmetry) then hemispheric dysfunction is indicated; if the asymmetry for
 387 stimulation of one eye reverses when the other eye is stimulated (crossed
 388 asymmetry), then a chiasmal anomaly is indicated.

389 Albinism and its associated excessive decussation of chiasmal fibres may lead to a
 390 crossed VEP asymmetry. The asymmetry is more conspicuous on monocular flash VEP
 391 testing in infants and becomes less conspicuous in older children and adults, where it
 392 is better seen using pattern reversal and onset stimulation. Previously, a crossed
 393 asymmetry was believed to be a prerequisite for the diagnosis of albinism. However,
 394 it is common to see children with genetically confirmed albinism but no crossed
 395 asymmetry. It seems that, for children with more severe albinism phenotypes (typical
 396 foveal hypoplasia, iris transillumination, skin and hair signs), crossed asymmetry is
 397 common and clear (and arguably unnecessary for the clinical diagnosis anyway),
 398 however for those with hypomorphic (less obvious) albinism phenotypes such as

399 OCA1b, crossing is far less reliable and as such its role in albinism diagnosis is often
400 limited.

401 Young infants with INS can present with large amplitude pendular nystagmus that
402 results in the infant appearing to have roving eyes. Electrodiagnostics are essential
403 to establish whether there is a visual pathway problem as well as to gain an insight
404 into the level of vision. Vertical and torsional nystagmus, as well as nystagmus that is
405 asymmetric when comparing the two eyes, is strongly associated with neurological
406 disease. However, such a typical nystagmus is seen in retinal dystrophies, CSNB,
407 albinism and idiopathic INS(40), indicating that although neuroimaging can be
408 necessary in such cases, non-invasive, electrodiagnostic studies remain important
409 and should be carried out in all such children.

410 It is important to note that the role of electrodiagnostics in children with nystagmus
411 goes beyond that of initial diagnosis alone (see figure 6).

412

413 **Figure 6**

414

415 *Diagnostic workflow*

416

417 When seeking a diagnosis for children with nystagmus, it is important to recognise
418 the limitations and inconsistent access to clinical equipment. For example, a 4-
419 month-old infant who has nystagmus, but for whom no other clinical information is
420 available, may have profound visual loss, a significant neurological disorder, albinism
421 or many other disorders. The degree of phenotyping (clinical
422 assessments/descriptions) dictates the ability to narrow the search for these groups

of disorders. Some clinical diagnostic tools are freely available (such as direct anterior and posterior segment examination) and some are scarcer (such as handheld OCT or electrodiagnostic). Most diagnostic workflows used in practice have the aim of streamlining the diagnostic process for as many children as possible by relying on the most freely available diagnostic tests and seeking the most urgent diagnoses as a priority. However, the inconsistency in approach has led to significant variations in clinical practice, sometimes including unnecessary invasive tests (such as Magnetic Resonance (MR) neuroimaging often requiring general anaesthesia) and a lack of resulting diagnosis for many infants/children. In practice, most diagnostic workflows seek to identify which of seven common patient groups children referred with nystagmus fall into as they broadly guide subsequent management or further investigation (see Table 4).

Table 4

As discussed in table 4, most patients following detailed clinical workup will fall into one of seven patient categories. However, the process of prioritising the investigations and the order in which they are completed varies significantly, partly due to the availability of clinical resources. In Figure 7, we propose a diagnostic workflow which forms the basis of our clinical practice across a number of specialist paediatric nystagmus services in the UK. It is important to note that this workflow focusses on the initial route to diagnosis only, and in many cases, additional tests will be required to support clinical management, for example VEP testing in order to quantify visual pathway lesions and visual prognosis in most cases.

Figure 7

449

450 *Genetic testing*

451

452 As detailed above, genetic testing forms a part of diagnosis for many children with
 453 nystagmus. Indeed, the role of genetic testing has changed significantly with the
 454 recent advent of multi-gene testing panels for clinical use. Currently, a variety of
 455 gene panels are relevant to children with nystagmus(41, 42). Clinical phenotyping is
 456 a necessary prerequisite in order to select the appropriate panel (e.g. a retinal
 457 dystrophy identified clinically might advocate a retinal, rather than an albinism, gene
 458 panel). NHS England is currently in a process of standardising these panels, and the
 459 genes which comprise them in addition to widening access to testing and
 460 centralising funding. Future approaches might differ from the current model, such as
 461 implementing much broader gene panel testing (such as those including all genes
 462 known to cause any eye disease) and using these as the first steps towards diagnosis
 463 with subsequent phenotyping employed to prove or disprove putative genetic
 464 diagnoses. These differing approaches are currently the topic of much debate, and
 465 clinicians will increasingly be required to understand the limitations of genetic testing
 466 along with its changing role in diagnostics, in many cases through closer
 467 collaboration with clinical genetic colleagues. Future directions are likely to be
 468 dictated by the cost and speed of genetic testing but will always require detailed
 469 clinical assessment in order to confirm or refute putative genetic diagnosis (which
 470 can be numerous when many genes are tested at once)(43) and direct future
 471 clinical care.

472

473 **Treatments and ongoing medical care**

474

475 *Refractive treatment*

476

477 Refractive correction is a priority when managing children with nystagmus. Contact
 478 lenses may be superior to glasses in improving visual function, due to a combination
 479 of optimal optical correction in a constantly moving eye, as well as an additional
 480 proprioceptive effect (see Table 5). Contact lenses can be helpful for patients with a
 481 significant refractive error and a significant AHP (as such patients otherwise tend to
 482 be limited by the frame of their glasses). Both rigid gas permeable (RGP) and soft
 483 contact lenses (SCL) are able to correct very large refractive errors and significant
 484 astigmatism (up to 15.00 DC with soft), although traditionally RGPs have been used
 485 in INS.

486

487 Prisms are an alternative form of refractive correction. By moving images, prisms can
 488 be used to exploit a convergence null, or null point/zone with a small associated
 489 compensatory head posture, either as short term pre-operative assessment or (far
 490 less commonly in the UK) as long term management.

491

492 To date, there are only two published randomised trials looking at refractive
 493 correction in INS, and a further 12 case reports/series (summarised in Table 5): eight
 494 looking at contact lens wear, three at prism therapy and one port-hole treatment.

495

496 Jayaramachandran *et al.* (2014)(44) reported a randomised, controlled cross-over
 497 trial with an intention-to-treat design comparing spectacles, SCL and RGP wear.

498 There was a total of 24 participants (12 idiopathic, 12 with albinism). There were no

499 significant differences in nystagmus intensity or any nystagmus parameter with either

contact lens wear compared with the baseline of spectacle wear. In fact, there was a worsening of near vision in both groups, despite a reduction in intensity.

Theodorou et al. (2018)(45) reported a pilot randomised control trial comparing fully corrective SCL with plano SCL in a group of 38 adult idiopaths. Despite the small effect size, there was an improvement in best corrected VA (BCVA) in both groups along with an improvement in some of the waveform parameters, in keeping with published data. However, due to the contrasting results, a larger randomised control trial is required to confirm/dispute the use of contact lenses as a safe evidence-based option for treatment in people of all ages, particularly in young children with greater plasticity in the visual cortex.

In the authors' experience, some children and young adults report good outcomes from contact lenses, particularly where high refractive errors are present and, as such, contact lenses should be considered, particularly in older children, but the possible benefit should be weighed against risks of CL related complications such as infection.

Table 5

Medical treatment

Baclofen, Gabapentin, Cannabis, Memantine, Aminopyridines and several other drugs have been used in acquired nystagmus(46-48). Baclofen has been shown to be useful in infantile Periodic Alternating Nystagmus (PAN). Gabapentin (up to 2400 mg in divided doses) and Memantine (up to 40 mg in divided doses) have been found to be useful in reducing nystagmus intensity in INS and in some patients to

increase VA(49). Both are usually well tolerated if the dose is increased slowly. Pregabalin has also been used in some cases, and Brinzolamide eye drops are gaining popularity worldwide but with limited supportive evidence. Most systemic drugs used to treat nystagmus, whether acquired or infantile, have significant side-effect profiles, and it is not clear which patients respond best, and at what age, and clearly larger clinical trials are needed before most are included in routine clinical practice. It is also worth noting that the aim of treatment varies widely between patients, for example those with INS and no oscillopsia and an adult with acute onset nystagmus and disabling oscillopsia. Most medical treatments have been used in patients over 16 years of age.

Surgical treatment

Current evidence suggests that the Kestenbaum-Anderson procedure is an effective treatment to correct anomalous head postures (AHP) occurring secondary to an eccentric null zone in INS. This is achieved by creating a gaze palsy in the preferred direction of gaze. (50-52) The classic procedure was modified by Parks(53) to the well-known “5, 6, 7, 8” procedure. Subsequently, it was recommended that the classic surgical amounts be augmented by 40% for AHPs up to 30° and 60% when an AHP exceeds 45°(54-59), or that a greater amount of symmetric surgery be performed (60-62). With these modifications, 72% to 100% of patients achieve an AHP of 15° or less postoperatively(54, 57, 59, 63-66). Smaller surgical amounts are required to correct a vertical AHP.(67) We recommend the simpler approach of performing large amounts of symmetric surgery, where possible (Table 6). Up to 43% of patients achieve increases in BCVA and up to a 60% reduction in recorded recognition times(59, 63, 68, 69) in some studies, but debate still exists particularly regarding

improvements in VA. Up to 40% of patients may require additional surgery after a mean interval of 6 years for under-corrections(70).

Preoperatively, an AHP should be evaluated by testing both with and without glasses at both distance and near, monocular and binocularly, noting the direction and degree of AHP adopted when maximal visual effort is exerted. Of particular importance is the identification of PAN, FMNS or co-existent strabismus, in which the recommended surgical approach needs to be altered. A standardised method for the objective measurement of the size of the AHP remains to be established, with many surgeons relying on photos and subjective estimates(71). Objective methods that can be used for measuring AHP, including using a cervical range of motion (CROM) device(72), orthopaedic goniometer(73), torticollometer, Harms' wall(74, 75) and other devices. More recently developed smartphone applications may also have a role in the evaluation of AHP(76) but are not in routine use currently.

AHP surgery during the pre-school years to optimise visual function and alleviate the cosmetic defect prior to this critical developmental period should be considered in children with significant torticollis (greater than 20°), which can be robustly measured and is consistent across several clinical visits(77).

Clinical tips:

As part of the pre-operative assessment of horizontal AHPs, all patients should be observed for at least 5 minutes to be certain one is not dealing with PAN. Additionally, the authors would generally advocate more than one repeat orthoptic examination and careful history taking regards head posture direction. Where the possibility of PAN arises from either, EMRs should be considered for confirmation. PAN has been noted to be common in albinism.

578

579 In INS, the use of a dynamic target, such as a video, can elicit AHPs that may not be evident on
580 testing of static VA.

581

582 **Table 6**

583

584 In the authors experience, significant duct ion deficits are rarely seen using this
585 surgical paradigm and avoiding a non-anchored hang-back technique in favour of
586 either direct scleral suture or anchored hang-back techniques.

587

588 *Ongoing management*

589

590 Due to the often-complex medical needs of children with nystagmus, continued
591 ophthalmic care is important; particularly for those with structural eye disorders, such
592 as retinal dystrophies or anterior segment dysgenesis, who may need Intraocular
593 pressure (IOP) checks or retinal therapies in addition to management of the
594 nystagmus. Orthoptic follow-up of children with nystagmus is needed to provide
595 timely identification and treatment of any associated amblyopia and management
596 of strabismus. Coexisting strabismus and amblyopia should be treated
597 conventionally, as appropriate for each individual, without specific changes to
598 account for the nystagmus(83, 84). Referral to paediatric low vision services is
599 recommended at an early stage, so that low vision aids can be introduced with
600 training to use them. Ongoing access to low vision and orthoptic services provides
601 an opportunity to support children and parents as they face new challenges, such
602 as starting nursery and full-time school, in both the provision of information and
603 updated management options depending on the child's needs.

A particularly difficult time for parents and older children is at discharge from hospital eye services to the general optical service. Lack of information transferring with the child often leads, at least, to difficult consultations for optometrists, but more concerning, to patients feeling that community-based eye-care practitioners don't understand their condition, losing their trust in the care received. In some instances, the lack of information transitioning with the patient leads to inappropriate re-referral and reinvestigation due to concerning 'new' findings that are long-standing but unknown to the referrer. Clear discharge information given to the patient is advised, including: a description of the nystagmus and any associated head posture, full diagnosis of the type of nystagmus and associated conditions, results of specific investigations carried out (e.g. genetic testing, EDTs, summary of treatments given, refractive correction, BCVA), and any certification completed (Severely Sight Impaired / Sight Impaired). Patient and GP combined ownership of this discharge report with clear support mechanisms for the future are vital in allowing patients to have positive experiences in subsequent participation in society and future eye care.

Patient support and resources

Information

It is hard to exaggerate the value of information about nystagmus and associated condition(s) to patients and their families(85). Generally, patients' questions fall into three categories: why do they or their child(ren) have nystagmus (cause), how will it affect them (impact), and what can be done about it (solution)?

Table 7

Knowing the cause has many benefits for patients. An accurate diagnosis empowers families to talk about nystagmus and advocate for themselves and/or their children. In addition, the wider family often wants to know the probability of others being born with nystagmus. Moreover, an accurate diagnosis will allow families to assess how future treatments may or may not benefit them, particularly as treatments are becoming more tailored to specific underlying aetiologies.

Parents especially want to understand the impact nystagmus has on their child. Their concerns typically include education, employment, driving and relationships (see Table 7). A realistic assessment of how nystagmus may affect each child is essential. Without it, parents will struggle to understand their needs and to make the necessary adaptations. Parents also have a vital role in explaining the impact of nystagmus to teachers and others involved in a child's education and development.

Over time, most patients accept that surgery and pharmaceuticals cannot cure nystagmus, although they may help in some cases. Nonetheless, it is important that patients fully understand the options available, including refraction and low vision aids, what will help, what will not help and why.

Clinicians may sometimes feel unable or lack the experience or time to answer some of these questions satisfactorily. It is important to recognise that national and local organisations exist to provide this support and reduce the strain on health services (see Table 8).

“Following the initial shock and panic, we did as most parents would do in this situation, and went against medical advice and consulted the internet for information. After scaring ourselves silly, we eventually came across the Nystagmus Network. ... We have found their support and advice invaluable in helping us to accept and understand the diagnosis better.” (Comment to NN helpline published in NN’s 2013 annual report).

Table 8

The role of Certificate of Vision Impairment (CVI) registration

Based on anecdotal evidence to the authors over 30 years, issuing a child or an adult who has nystagmus with a CVI (Certificate of Vision Impairment) is in most cases a great help. Although the concrete benefits may appear limited, in practice, having a CVI enables patients to access support they may otherwise be denied. For instance, it is now difficult for a child with nystagmus to get an EHCP (Education Health and Care Plan) without first having a CVI.

A CVI also helps in accessing sports and entertainment venues, obtaining travel concessions and using the DWP’s (Department of Work and Pensions) Access to Work scheme. Very few patients find CVIs a stigma. Patients can choose to revoke their CVI, for example if vision is good enough to apply for a driving licence at age 17.

“Having been spurred on by your advice I mentioned the various difficulties to my optician the next time I went. She referred me to the local hospital where I saw an

ophthalmologist who immediately said I should be registered visually impaired. The process was much easier than I imagined.” (Comment to NN helpline published in NN’s 2014 annual report).

685

Patient perspective

687

Ideally, when patients are discharged from hospital they should have a realistic understanding of the impact nystagmus will have on them or their child. This should extend beyond VA and include the null zone, the difficulties caused by clutter/crowding and movement, the additional time needed to see (slow-to-see phenomenon), the variability of vision and whether or not the nystagmus is part of a progressive or largely static condition. Often simple things can have a great impact such as sitting children in class in a position in which they can utilise, rather than be penalised, by their null zone.

696

Patients should also be aware of the potential social impacts of nystagmus. For instance, research(86) suggests that the cosmetic consequences of nystagmus (abnormal head posture, flickering eyes, difficulty making eye contact) are underestimated and contribute to feelings of isolation, low self-esteem and depression.

701

The challenge for clinicians, at a time when we are still learning about the impacts of nystagmus and how to measure them, is knowing where to strike the correct balance. On the one hand, patients should not be discharged thinking “nystagmus is the end of the world”. On the other hand, they should not leave a hospital eye department thinking nystagmus will have no impact at all.

707

708 **Summary**

709

710 Children with nystagmus are not uncommon in paediatric ophthalmic practice.
711 Despite this, investigation and clinical management can vary widely across the UK
712 and beyond. It seems likely that this is due to a potent combination of clinical
713 concern regarding urgent underlying causes, subtlety to the clinical examination,
714 variability of clinical picture and limited understanding of the mechanisms involved
715 in causality. Herein, we hope to provide some information to clinicians on how
716 children with nystagmus are currently managed in specialist centres in the UK and
717 highlight the view of patients and their families. We hope that this will help us move
718 towards improved health equity across UK centres for children with nystagmus and
719 demystify what is often a relatively straight-forward, methodical approach.

720

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722

References

1. Sarvananthan N, Surendran M, Roberts EO, Jain S, Thomas S, Shah N, et al. The prevalence of nystagmus: the Leicestershire nystagmus survey. *Invest Ophthalmol Vis Sci*. 2009;50(11):5201-6.
2. Gottlob I, Zubcov A, Catalano RA, Reinecke RD, Koller HP, Calhoun JH, et al. Signs distinguishing spasmus nutans (with and without central nervous system lesions) from infantile nystagmus. *Ophthalmology*. 1990;97(9):1166-75.
3. Leigh RJ, Zee DS. *The Neurology of Eye Movements*: New York: Oxford University Press; 2006.
4. Casteels I, Harris CM, Shawkat F, Taylor D. Nystagmus in infancy. *BrJOphthalmol*. 1992;76(7):434-7.
5. Osborne D, Theodorou M, Lee H, Ranger M, Hedley-Lewis M, Shawkat F, et al. Supranuclear eye movements and nystagmus in children: A review of the literature and guide to clinical examination, interpretation of findings and age-appropriate norms. *Eye (Lond)*. 2019;33(2):261-73.
6. Brodsky MC, Fray KJ. The prevalence of strabismus in congenital nystagmus: the influence of anterior visual pathway disease. *JAAPOS*. 1997;1(1):16-9.
7. Dell'Osso LF. Congenital, latent and manifest latent nystagmus--similarities, differences and relation to strabismus. *JpnJOphthalmol*. 1985;29(4):351-68.
8. Abadi RV, Dickinson CM. Waveform characteristics in congenital nystagmus. *DocOphthalmol*. 1986;64(2):153-67.
9. Dell'Osso LF, Flynn JT, Daroff RB. Hereditary congenital nystagmus. An intrafamilial study. *ArchOphthalmol*. 1974;92(5):366-74.

- 746 10. Brodsky MC, Fray KJ. Positive angle kappa: a sign of albinism in patients with
747 congenital nystagmus. *AmJOphtalmol*. 2004;137(4):625-9.
- 748 11. Osborne D, Theodorou M, Lee H, Ranger M, Hedley-Lewis M, Shawkat F, et al.
749 Supranuclear eye movements and nystagmus in children: A review of the literature and
750 guide to clinical examination, interpretation of findings and age-appropriate norms. *Eye*.
751 2019;33(2):261-73.
- 752 12. Hove MN, Kilic-Biyik KZ, Trotter A, Grønskov K, Sander B, Larsen M, et al. Clinical
753 Characteristics, Mutation Spectrum, and Prevalence of Åland Eye Disease/Incomplete
754 Congenital Stationary Night Blindness in Denmark. *Invest Ophthalmol Vis Sci*.
755 2016;57(15):6861-9.
- 756 13. Benouaich X, Mahieu L, Matonti F, Soler V. Persistence of foveal capillary plexi in a
757 case of fovea plana evident on OCT angiography. *J Fr Ophtalmol*. 2017;40(1):4-7.
- 758 14. Bowl W, Andrassi-Darida M, Holve K, Schweinfurth S, Knobloch R, Lorenz B.
759 [Handheld Optical Coherence Tomography in Paediatric Ophthalmology: Experience of the
760 Department of Ophthalmology in Giessen]. *Klin Monbl Augenheilkd*. 2016;233(10):1142-8.
- 761 15. Sánchez-Vicente JL, Contreras-Díaz M, Llerena-Manzorro L, Rueda T, López-Herrero
762 F, Molina-Socola FE, et al. FOVEAL HYPOPLASIA: DIAGNOSIS USING OPTICAL COHERENCE
763 TOMOGRAPHY ANGIOGRAPHY. *Retin Cases Brief Rep*. 2018;12(2):122-6.
- 764 16. Langlo CS, Patterson EJ, Higgins BP, Summerfelt P, Razeen MM, Erker LR, et al.
765 Residual Foveal Cone Structure in CNGB3-Associated Achromatopsia. *Invest Ophthalmol Vis*
766 *Sci*. 2016;57(10):3984-95.
- 767 17. Lee H, Proudlock FA, Gottlob I. Pediatric Optical Coherence Tomography in Clinical
768 Practice-Recent Progress. *Invest Ophthalmol Vis Sci*. 2016;57(9):OCT69-79.

- 769 18. Kumar V, Molla K, Chandra P, Kumar A. Dome-shaped macula in oculocutaneous
770 albinism. *BMJ Case Rep.* 2016;2016.
- 771 19. Al Oreany AA, Al Hadlaq A, Schatz P. Congenital stationary night blindness with
772 hypoplastic discs, negative electroretinogram and thinning of the inner nuclear layer.
773 *Graefes Arch Clin Exp Ophthalmol.* 2016;254(10):1951-6.
- 774 20. Bouraoui R, Bouladi M, Nefaa F, Limaïem R, El Matri L. [Role of SD-OCT in the
775 diagnosis and prognosis of macular hypoplasia in nystagmus patients]. *J Fr Ophthalmol.*
776 2016;39(3):272-6.
- 777 21. Matalia J, Rajput VK, Chillal GJ, Shetty BK. Upbeat nystagmus in a 3.5-year-old boy. *J*
778 *AAPOS.* 2016;20(1):88-90.
- 779 22. Hull S, Arno G, Holder GE, Plagnol V, Gomez K, Liesner R, et al. The ophthalmic
780 presentation of Hermansky-Pudlak syndrome 6. *Br J Ophthalmol.* 2016;100(11):1521-4.
- 781 23. Mallipatna A, Vinekar A, Jayadev C, Dabir S, Sivakumar M, Krishnan N, et al. The use
782 of handheld spectral domain optical coherence tomography in pediatric ophthalmology
783 practice: Our experience of 975 infants and children. *Indian J Ophthalmol.* 2015;63(7):586-
784 93.
- 785 24. Mohammad S, Gottlob I, Sheth V, Pilat A, Lee H, Pollheimer E, et al. Characterization
786 of Abnormal Optic Nerve Head Morphology in Albinism Using Optical Coherence
787 Tomography. *Invest Ophthalmol Vis Sci.* 2015;56(8):4611-8.
- 788 25. Han R, Wang X, Wang D, Wang L, Yuan Z, Ying M, et al. GPR143 Gene Mutations in
789 Five Chinese Families with X-linked Congenital Nystagmus. *Sci Rep.* 2015;5:12031.
- 790 26. McCafferty BK, Wilk MA, McAllister JT, Stepien KE, Dubis AM, Brilliant MH, et al.
791 Clinical Insights Into Foveal Morphology in Albinism. *J Pediatr Ophthalmol Strabismus.*
792 2015;52(3):167-72.

- 793 27. Putnam CM, Bland PJ. Macular pigment optical density spatial distribution measured
794 in a subject with oculocutaneous albinism. *J Optom.* 2014;7(4):241-5.
- 795 28. Cornish KS, Reddy AR, McBain VA. Concentric macular rings sign in patients with
796 foveal hypoplasia. *JAMA Ophthalmol.* 2014;132(9):1084-8.
- 797 29. Cai CY, Zhu H, Shi W, Su L, Shi O, Cai CQ, et al. A novel splicing site mutation of the
798 GPR143 gene in a Chinese X-linked ocular albinism pedigree. *Genet Mol Res.*
799 2013;12(4):5673-9.
- 800 30. Thomas S, Thomas MG, Andrews C, Chan WM, Proudlock FA, McLean RJ, et al.
801 Autosomal-dominant nystagmus, foveal hypoplasia and presenile cataract associated with a
802 novel PAX6 mutation. *Eur J Hum Genet.* 2014;22(3):344-9.
- 803 31. Lee H, Purohit R, Sheth V, McLean RJ, Kohl S, Leroy BP, et al. Retinal Development in
804 Infants and Young Children with Achromatopsia. *Ophthalmology.* 2015.
- 805 32. Lee H, Sheth V, Bibi M, Maconachie G, Patel A, McLean RJ, et al. Potential of
806 handheld optical coherence tomography to determine cause of infantile nystagmus in
807 children by using foveal morphology. *Ophthalmology.* 2013;120(12):2714-24.
- 808 33. Lee H, Proudlock F, Gottlob I. Is handheld optical coherence tomography reliable in
809 infants and young children with and without nystagmus? *Investigative ophthalmology &*
810 *visual science.* 2013;54(13):8152-9.
- 811 34. Thomas MG, Kumar A, Mohammad S, Proudlock FA, Engle EC, Andrews C, et al.
812 Structural grading of foveal hypoplasia using spectral-domain optical coherence tomography
813 a predictor of visual acuity? *Ophthalmology.* 2011;118(8):1653-60.
- 814 35. Clark R, Blundell J, Dunn MJ, Erichsen JT, Giardini ME, Gottlob I, et al. The potential
815 and value of objective eye tracking in the ophthalmology clinic. *Eye (Lond).*
816 2019;33(8):1200-2.

- 817 36. Dell'Osso L, Gauthier G, Liberman G, Stark L. Eye movement recordings as a
818 diagnostic tool in a case of congenital nystagmus. *AmJOptomArchAmAcadOptom*.
819 1972;49(1):3-13.
- 820 37. Ramat S, Leigh RJ, Zee DS, Shaikh AG, Optican LM. Applying saccade models to
821 account for oscillations. *Prog Brain Res*. 2008;171:123-30.
- 822 38. Kriss A, Russell-Eggitt I. Electrophysiological assessment of visual pathway function in
823 infants. *Eye (Lond)*. 1992;6 (Pt 2):145-53.
- 824 39. McCulloch DL, Marmor MF, Brigell MG, Hamilton R, Holder GE, Tzekov R, et al.
825 Erratum to: ISCEV Standard for full-field clinical electroretinography (2015 update). *Doc*
826 *Ophthalmol*. 2015;131(1):81-3.
- 827 40. Shawkat FS, Kriss A, Thompson D, Russell-Eggitt I, Taylor D, Harris C. Vertical or
828 asymmetric nystagmus need not imply neurological disease. *BrJOphthalmol*.
829 2000;84(2):175-80.
- 830 41. O'Gorman L, Norman CS, Michaels L, Newall T, Crosby AH, Mattocks C, et al. A small
831 gene sequencing panel realises a high diagnostic rate in patients with congenital nystagmus
832 following basic phenotyping. *Sci Rep*. 2019;9(1):13229.
- 833 42. Thomas MG, Maconachie G, Sheth V, McLean RJ, Gottlob I. Development and clinical
834 utility of a novel diagnostic nystagmus gene panel using targeted next-generation
835 sequencing. *Eur J Hum Genet*. 2017;25(6):725-34.
- 836 43. Norman CS, O'Gorman L, Gibson J, Pengelly RJ, Baralle D, Ratnayaka JA, et al.
837 Identification of a functionally significant tri-allelic genotype in the Tyrosinase gene (TYR)
838 causing hypomorphic oculocutaneous albinism (OCA1B). *Sci Rep*. 2017;7(1):4415.

- 839 44. Jayaramachandran P, Proudlock FA, Odedra N, Gottlob I, McLean RJ. A randomized
840 controlled trial comparing soft contact lens and rigid gas-permeable lens wearing in infantile
841 nystagmus. *Ophthalmology*. 2014;121(9):1827-36.
- 842 45. Theodorou M, Quartilho A, Xing W, Bunce C, Rubin G, Adams G, et al. Soft Contact
843 Lenses to Optimize Vision in Adults with Idiopathic Infantile Nystagmus: A Pilot Parallel
844 Randomized Controlled Trial. *Strabismus*. 2018;26(1):11-21.
- 845 46. Mehta AR, Kennard C. The pharmacological treatment of acquired nystagmus. *Pract*
846 *Neurol*. 2012;12(3):147-53.
- 847 47. Kalla R, Strupp M. Aminopyridines and Acetyl-DL-leucine: New Therapies in
848 Cerebellar Disorders. *Curr Neuropharmacol*. 2019;17(1):7-13.
- 849 48. McLean RJ, Gottlob I. The pharmacological treatment of nystagmus: a review. *Expert*
850 *Opin Pharmacother*. 2009;10(11):1805-16.
- 851 49. McLean R, Proudlock F, Thomas S, Degg C, Gottlob I. Congenital nystagmus:
852 randomized, controlled, double-masked trial of memantine/gabapentin. *Annals of*
853 *neurology*. 2007;61(2):130-8.
- 854 50. ANDERSON JR. Causes and treatment of congenital eccentric nystagmus. *Br J*
855 *Ophthalmol*. 1953;37(5):267-81.
- 856 51. Goto N. A study of optic nystagmus by the electro-oculogram. 1954;58:851-65.
- 857 52. Kestenbaum A. Nouvelle operation du nystagmus. 1954;2:851-65.
- 858 53. Parks MM. Symposium: nystagmus. Congenital nystagmus surgery. *Am Orthopt J*.
859 1973;23:35-9.
- 860 54. Nelson LB, Ervin-Mulvey LD, Calhoun JH, Harley RD, Keisler MS. Surgical
861 management for abnormal head position in nystagmus: the augmented modified
862 Kestenbaum procedure. *Br J Ophthalmol*. 1984;68(11):796-800.

- 863 55. Calhoun JH, Harley RD. Surgery for abnormal head position in congenital nystagmus.
864 Transactions of the American Ophthalmological Society. 1973;71:70-83; discussion 4-7.
- 865 56. Kang NY, Isenberg SJ. Kestenbaum procedure with posterior fixation suture for
866 anomalous head posture in infantile nystagmus. Graefes Arch Clin Exp Ophthalmol.
867 2009;247(7):981-7.
- 868 57. Lee IS, Lee JB, Kim HS, Lew H, Han SH. Modified Kestenbaum surgery for correction
869 of abnormal head posture in infantile nystagmus: outcome in 63 patients with graded
870 augmentaton. Binocul Vis Strabismus Q. 2000;15(1):53-8.
- 871 58. Taylor JN, Jesse K. Surgical management of congenital nystagmus. Aust N Z J
872 Ophthalmol. 1987;15(1):25-34.
- 873 59. Scott WE, Kraft SP. Surgical treatment of compensatory head position in congenital
874 nystagmus. J Pediatr Ophthalmol Strabismus. 1984;21(3):85-95.
- 875 60. Schild AM, Thoenes J, Fricke J, Neugebauer A. Kestenbaum procedure with combined
876 muscle resection and tucking for nystagmus-related head turn. Graefes Arch Clin Exp
877 Ophthalmol. 2013;251(12):2803-9.
- 878 61. Kommerell G. [Surgical management of altered head posture in patients with
879 congenital nystagmus (author's transl)]. Klinische Monatsblätter für Augenheilkunde.
880 1974;164(2):172-91.
- 881 62. Pratt-Johnson JA. Results of surgery to modify the null-zone position in congenital
882 nystagmus. Can J Ophthalmol. 1991;26(4):219-23.
- 883 63. Sandall GS. Surgical treatment of congenital nystagmus in patients with singular
884 binocular vision. Annals of ophthalmology. 1976;8(2):227-38.
- 885 64. Kraft SP, O'Donoghue EP, Roarty JD. Improvement of compensatory head postures
886 after strabismus surgery. Ophthalmology. 1992;99(8):1301-8.

- 887 65. Chang YH, Chang JH, Han SH, Lee JB. Outcome study of two standard and graduated
888 augmented modified Kestenbaum surgery protocols for abnormal head postures in infantile
889 nystagmus. *Binocular vision & strabismus quarterly*. 2007;22(4):235-41.
- 890 66. Biglan AW, Hiles DA, Ying-Fen Z, Kortvelesy JS, Pettapiece MC.
- 891 67. Spielmann A. Clinical rationale for manifest congenital nystagmus surgery. *J Aapos*.
892 2000;4(2):67-74.
- 893 68. Kumar A, Shetty S, Vijayalakshmi P, Hertle RW. Improvement in visual acuity
894 following surgery for correction of head posture in infantile nystagmus syndrome. *J Pediatr*
895 *Ophthalmol Strabismus*. 2011;48(6):341-6.
- 896 69. ElKamshoushy A, Shawky D, ElMassry A, ElBaha S, Abdel Wahab MM, Sprunger D.
897 Improved visual acuity and recognition time in nystagmus patients following four-muscle
898 recession or Kestenbaum-Anderson procedures. *J Aapos*. 2012;16(1):36-40.
- 899 70. Biglan AW, Hiles DA, Ying-Fen Z, Kortvelesy JS, Pettapiece MC. Results after Surgery
900 for Null Point Nystagmus with Abnormal Head Position. *American Orthoptic Journal*.
901 1989;39(1):134-42.
- 902 71. Lee J. Surgical management of nystagmus. *J R Soc Med*. 2002;95(5):238-41.
- 903 72. Kushner BJ. The usefulness of the cervical range of motion device in the ocular
904 motility examination. *Arch Ophthalmol*. 2000;118(7):946-50.
- 905 73. Mitchell PR, Wheeler MB, Parks MM. Kestenbaum surgical procedure for torticollis
906 secondary to congenital nystagmus. *J Pediatr Ophthalmol Strabismus*. 1987;24(2):87-93.
- 907 74. Tyedmers M, Roper-Hall G. The harms tangent screen test. *Am Orthopt J*.
908 2006;56:175-9.
- 909 75. Harms H. Ueber die Untersuchung der Augenmuskellahmungen. *Graefes Arch*
910 *Ophthalmol* 1941; 144: 129. 1941;144:129.

- 911 76. Pourahmadi MR, Bagheri R, Taghipour M, Takamjani IE, Sarrafzadeh J, Mohseni-
912 Bandpei MA. A new iPhone application for measuring active craniocervical range of motion
913 in patients with non-specific neck pain: a reliability and validity study. *Spine J.*
914 2018;18(3):447-57.
- 915 77. Dell'Osso LF, Flynn JT. Congenital nystagmus surgery. A quantitative evaluation of
916 the effects. *Arch Ophthalmol.* 1979;97(3):462-9.
- 917 78. Gräf M, Droutsas K, Kaufmann H. [Congenital nystagmus: indication, results and
918 dosage of Kestenbaum surgery in 34 patients]. *Klinische Monatsblätter für Augenheilkunde.*
919 2000;217(6):334-9.
- 920 79. Wang P, Lou L, Song L. Design and efficacy of surgery for horizontal idiopathic
921 nystagmus with abnormal head posture and strabismus. *Journal of Huazhong University of*
922 *Science and Technology Medical sciences = Hua zhong ke ji da xue xue bao Yi xue Ying De*
923 *wen ban = Huazhong keji daxue xuebao Yixue Yingdewen ban.* 2011;31(5):678-81.
- 924 80. von Noorden GK, Sprunger DT. Large rectus muscle recessions for the treatment of
925 congenital nystagmus. *Arch Ophthalmol.* 1991;109(2):221-4.
- 926 81. Arruga A. Posterior fixation of recti in nystagmus with retinal detachment. *Mod Probl*
927 *Ophthalmol.* 1975;15:304-6.
- 928 82. Mühlendyck H, Linnen HJ. [The operative treatment of nystagmus-caused variable
929 squint angles with Cüppers "Fadenoperation" (author's transl)]. *Klinische Monatsblätter für*
930 *Augenheilkunde.* 1975;167(2):273-90.
- 931 83. von Noorden GK, Avilla C, Sidikaro Y, LaRoche R. Latent nystagmus and strabismic
932 amblyopia. *Am J Ophthalmol.* 1987;103(1):87-9.
- 933 84. Thurtell MJ, Leigh RJ. Therapy for nystagmus. *J Neuroophthalmol.* 2010;30(4):361-
934 71.

- 935 85. Bjerre A, Arblaster, G.E., Nye, A. and Griffiths, H.J. The Provision of Patient
936 Information about Nystagmus. British and Irish Orthoptic Journal. 2018(14(1)):25-9.
- 937 86. McLean RJ, Windridge KC, Gottlob I. Living with nystagmus: a qualitative study. Br J
938 Ophthalmol. 2012;96(7):981-6.
- 939

| Question | Clinical relevance |
|---|---|
| Pregnancy, maternal medication/drug use and birth history | Maternal drug exposure and prematurity have been associated with nystagmus. |
| Family history of eye/neurological disease/systemic disease | Many eye movement disorders have a hereditary component with different inheritance patterns indicating which genes may be involved. |
| Pigmentation in skin and hair compared to rest of family | Albinism is a common underlying associated disorder, but sometimes without a definite family history. |
| Specific questions about visual behaviours – e.g. nyctalopia or photophobia | Photophobia and nystagmus are common findings in disorders of cone function and albinism. High frequency low amplitude nystagmus with photophobia is more common in cone dysfunction. Nyctalopia is a common symptom in rod dysfunction. |
| Open questioning about other visual behaviours | Parents will often report a very detailed description of visual behaviours, which can direct clinical examination such as a child with chin depression and vertically ‘wobbly eyes’ (commonly seen in downbeat nystagmus), or pushing/rubbing eyes firmly for retinal stimulation in blind babies/children. |
| Does the child experience oscillopsia? | Lack of oscillopsia in the presence of involuntary eye movements such as nystagmus in an older child suggests early-onset. Infrequent episodes of oscillopsia despite a constant nystagmus is also seen in early-onset nystagmus. Constant oscillopsia suggests an acquired disorder. |
| If oscillopsia is reported, is it when stationary or when moving? | Oscillopsia, which is only present during head movement, implies a vestibular pathology. |
| Are there associated speech or swallowing problems? | Possible brainstem pathology or myasthenia gravis |
| Are there associated coordination problems? | Possible cerebellar pathology |
| Is there associated hearing loss or tinnitus? | Possible peripheral vestibular pathology |

| | |
|--|---|
| Is the patient on any medications? | Many medications can cause abnormalities of eye movement, most commonly anti-epileptic medication. |
| Are there any concerns about any other aspect of the child's development or health besides their eyes? | Eye movement abnormalities form a part of many multisystem syndromes and can be the presenting feature. |
| At what age did the parent/carer notice the nystagmus? | INS is typically noticed in the first 4-6 months of life but it's typical onset (when seeking it in at risk patients) is 1.9 months(2). |

Table 1: History taking in an infant/child presenting with nystagmus

| | |
|-----------------------------------|---|
| Idiopathic INS | Sometimes family history (typically X-linked). Conjugate, typically horizontal nystagmus, may dampen on convergence, +/- head shake, +/- one/alternating null point, in an otherwise well infant child with normal eyes and systemic examination. |
| Oculo-cutaneous / ocular albinism | Often family history, typically less pigmentation in hair and skin, hypopigmented iris pigment epithelium (often transillumination) and retinal pigment epithelium, tilted discs and foveal hypoplasia. Evidence of chiasmal misrouting. |
| PAX6 gene disorders | Often family history, corneal epitheliopathy, early onset lens opacity, varying degrees of iris hypoplasia (near normal to aniridic), foveal hypoplasia. No evidence of chiasmal misrouting. |
| Achromatopsia | Often family history, photophobia, reduced/absent colour vision, nystagmus typically 'fine or shimmering' grossly normal macula appearance (may have retinal pigment epithelium (RPE) changes/atrophy). |

Table 2: Classic presentation of common ophthalmic conditions associated with INS: key points

| Clinical Test | Description |
|-------------------------|--|
| Head posture | <ul style="list-style-type: none"> • Presence and degree of any Anomalous Head Posture (AHP) should be recorded – including a description for both near and distance fixation, with and ideally without any refractive correction. • Any change with visual demand should be noted. • Presence or absence of any involuntary head nodding should be recorded with activity in which this occurs. |
| VA | <ul style="list-style-type: none"> • With refractive correction – both eyes open and monocularly • A note taken as to whether measured with or without head posture • Near using preferred reading distance and distance • Record method of occlusion, e.g. opaque occluder / high plus lens |
| Cover test | <ul style="list-style-type: none"> • With and without refractive correction • With and without AHP • Near and distance fixation • Note presence or absence of nystagmus, any change in amplitude and/or direction of nystagmus on covering one eye. |
| Binocular single vision | <ul style="list-style-type: none"> • With refractive correction and any AHP • Sensory, motor fusion for near and distance fixation • Presence or absence of stereopsis - stereoacuity when possible • Note AHP adopted to achieve binocular responses. |
| Ocular movements | <ul style="list-style-type: none"> • Testing of ductions and versions in nine positions of gaze for near fixation, with description of nystagmus in primary and secondary positions. • VOR (vertical and horizontal) – presence/absence • Optokinetic nystagmus (OKN) – presence/ absence / abnormal (expected or inverted response) • Smooth pursuit – horizontal and vertical • [for detail of methods of testing, see Osborne et al., 2019(5)] |
| Convergence | <ul style="list-style-type: none"> • With refractive correction with AHP – noting ability to convergence and change in amplitude and/or frequency of nystagmus |

| | |
|--------------------------|--|
| Measurement of deviation | <ul style="list-style-type: none"> • If possible, using alternating prism cover test – with refractive correction, with and without AHP • Near and at distance – primary position, secondary positions if indicated to document change from primary position or to confirm concomitance • Individual reading position if different from above |
|--------------------------|--|

Table 3: Orthoptic assessment in children with nystagmus

| Patient cohort | Description |
|---|--|
| Idiopathic Infantile Nystagmus Syndrome (IINS) | Seen in patients with no apparent cause for nystagmus either systemically or after detailed ocular examination. Typical clinical features include onset between 4-6 months of age, horizontal nystagmus, staying horizontal in vertical gaze, beating in the direction of gaze, dampening on convergence and associated with null zones and head postures. Typically, further investigation would include electrodiagnostics, OCT and genetic testing but not MRI brain imaging. |
| Nystagmus due to inherited retinal dystrophy | Clinical features may include photophobia, nyctalopia, and very low VA. The nystagmus can be multiphasic and often high intensity (fast and small amplitude). Typically, further investigation would include electrodiagnostics, OCT and either retinal gene panel testing or additional retinal phenotyping but not MRI brain imaging. |
| Nystagmus with abnormal ocular findings (not retinal dystrophy) | Often subtle signs suggesting a group of underlying disorders such as iris transillumination or foveal hypoplasia suggesting hypomorphic forms of <i>PAX6</i> gene disease, mutations in <i>SLC38A8</i> or albinism spectrum disorders. Further investigation would typically include additional ocular or non-ocular phenotyping, VEP and OCT or bespoke genetic testing and not MRI brain imaging. |
| Fusion Maldevelopment Nystagmus Syndrome (FMNS, previously MLN) | Caused by early loss of binocularity and seen very commonly in strabismus, congenital cataract and any cause of early visual loss. Typical clinical features include horizontal nystagmus which beats in the direction of the viewing eye with monocular occlusion and which dampens in adduction of the viewing eye. Typically, no further investigation is required. |
| Acquired nystagmus or those with significant oscillopsia | As these cases are rarely caused by true congenital genetic disorders, most warrant systemic, investigation in the first instance. Clinical features may include an older patient (or child older than 6 months) with recent onset nystagmus, not beating in the direction of gaze and associated with oscillopsia. Typically, MR neuroimaging would form an early part in further investigation in addition to electrodiagnostics. |
| Nystagmus in a patient with very poor vision from infancy (not retinal dystrophy) | As any cause of poor vision in infants can cause a stimulus deprivation nystagmus (such as congenital cataract or optic nerve hypoplasia). Clinical features may include obvious clinical signs and very poor vision with nystagmus of varying forms. Further investigation would be directed by the findings and typically include electrodiagnostics to assess post-retinal and chiasmal integrity as well as levels of vision. |
| Non-nystagmus eye movement disorders | Such as abnormal square-wave jerks, psychogenic flutter, opsoclonus or ocular flutter. These disorders can be misdiagnosed as nystagmus but have different aetiologies and investigation pathways according to findings. |

Table 4: Seven of the most common patient cohorts into which most children presenting with nystagmus fall. These cohorts broadly dictate the next line of investigation of management, and clinical investigation workflows are designed in order to arrive at one of these broad diagnostic categories for most patients.

| Title | Author, Year | Study & Intervention | Results |
|--|---------------------|---|---|
| Contact lens application in four cases of congenital nystagmus | Hale 1962 | Retrospective case series: four patients with INS Intervention: Contact lens | |
| Prism Exploitation of Gaze and Fusional Null Angles in Congenital Nystagmus | Dell'Osso 1976 | Study design: Case series (four patients 27-41 yo) Interventions: Refraction correction with spectacles and prism | All four adults had prisms prescribed to provide a shift in the null zone, with an improvement in binocular Snellen VA. |
| Role of contact lenses in the management of congenital nystagmus | Allen 1983 | Retrospective case series over 7 years. Eight patients (10-43 yo) with INS (three associated albinism). No randomisation or masking. Interventions: Contact lenses: Some initially soft, all patients ended with hard contact lenses | 13 eyes: ≥ 1 line improvement, five eyes ≥ 3 lines improvement |
| The port-hole method in the treatment of congenital nystagmus | Sasso 1986 | Case series: 38 children Intervention: Port-hole treatment (peripheral occlusion) for five years | Improved VA and recordings |
| The application of hard contact lenses in patients with congenital nystagmus | Golubovic 1989 | Retrospective case series: 112 patients with nystagmus with either myopia or mixed form of astigmatism Intervention: Hard contact lens wear | 210 contact lenses were fitted in 112 patients. VA improved significantly in the 79% who with correction of refractive error with CLs. Well tolerated in all. |
| Intermittent Oscillopsia in a Case of Congenital Nystagmus, Dependence Upon Waveform | Abel 1991 | Case Report (one patient with INS, 14 yo), two visits 2 weeks apart Interventions: Contact lenses and anaesthesia | Stable image with contact lenses (with/without anaesthesia). Drift velocity was $<4^\circ/\text{sec}$ and foveation duration was >100 msec. |

| | | | |
|--|--------------|--|--|
| Congenital nystagmus: rebound phenomenon following removal of contact lenses | Saffran 1992 | Case report (one patient, 20 yo) with INS Interventions: Contact lens wear (90 minute trial) | Patient experienced transient dizziness attributed to oscillopsia following intervention. |
| The use of contact lenses to treat visually symptomatic congenital nystagmus | Biousse 2004 | Prospective case series. four participants patients (18-64 yo) with INS (two associated albinism) Interventions: SCL wear (versus spectacle wear) | Improvement VA (mean BCVA 20/64 to 20/40), contrast sensitivity and VFQ-25 scores. Several parameters of nystagmus showed no change in two patients participants, worsening in one patient and improvement in one patient. |
| Soft Contact lenses to improve motor and sensory function in congenital nystagmus | Rutner 2005 | Case report (1 patient, 18 yo). IN associated with albinism. Interventions: SCL (CooperVision Preference Toric) Intervention: Spectacles v SCL v SCL with anaesthetic (1 week) | Results: Improvement in Snellen and Bailey-Lovie VA 1 week post SCL wear. Reduced amplitude and frequency with SCL (increased with anaesthetic) - persistent reduction in amplitude after 1 week. |
| Combined gaze-angle and vergence variation in INS: two therapies that improve the high-visual-acuity field and methods to measure it | Serra 2006 | Case report (two patients, only one optical intervention) Intervention: Base out prisms (convergence null) | Improved NAFX at null, and broadened null region |

| | | | |
|---|--------------|---|--|
| Preliminary observation on the effect of pressing triple prism in correcting residual compensatory head posture after congenital nystagmus surgery. | Tang 2013 | Case series (28 children, 4-20 yo, residual AHP post surgery) Intervention: Pressing triple prism. | 1/28 lost to follow up. Improvement in VA (not statistically significant), and AHP (statistically significant) in 26/27 - 18/27 had resolution (<5 degrees). |
| Effect of Rigid Gas Permeable Contact Lenses on Nystagmus and Visual Function in Hyperopic Patients with INS | Bagheri 2017 | Prospective interventional case series: 16 participants with INS and hyperopia more than/equal to +0.50 D and astigmatism more than -1.00 D Intervention: RGP for 3 months | RGPs fitted in 16 participants. Improvement in VA, contrast sensitivity and motor indices of nystagmus. |

Table 5: A summary of literature on the use of contact lenses in adults and children with nystagmus

| Horizontal AHP | Abducting eye | Adducting eye |
|---|--|--|
| A minimum dosage (in mm) on each eye of 2/3 the AHP (in degrees) is recommended.(78) | | |
| Mild 24° to 30° | LRc(-) & MRs(+) 8.0 to 10.0mm | MRc(-) & LRs(+) 8.0 to 10.0mm |
| Moderate 30° to 36° | LRc(-) & MRs(+) 10.0 to 12.0mm | MRc(-) & LRs(+) 10.0 to 12.0mm |
| Severe >36° | LRc(-) & MRs(+) 12.0 to 14.0mm | MRc(-) & LRs(+) 12.0 to 14.0mm |
| Graded Anderson | Lateral Rectus Recession | Medial Rectus Recession |
| Minimal 15° | 10.0 mm | 7.0 mm |
| Mild 20° to 25° | 11.0 mm | 8.0 mm |
| Moderate 30° | 12.0 mm | 9.0 mm |
| Moderate to Severe 35° (30° to 40°) | 10.0 to 17.0 mm | 13.0 to 15.0 mm |
| In the presence of FMNS or a tropia, surgery should be performed on the fixing eye, with surgery for any residual heterotropia performed on the non-fixing eye.(55, 79) | | |
| Vertical AHP | Superior Recti BE | Inferior Recti BE |
| A minimum dosage (in mm) on each eye of approximately 1/4 of the amount of head elevation/depression (in degrees) is recommended.(78) | | |
| Chin-up 32° to 40° | | IRc(-) 8.0 to 10.0mm* |
| Chin-down 32° to 40° | SRc(-) 8.0 to 10.0mm | |
| Chin-up >40° | | IRc(-) 10.0 to 12.0mm* |
| Chin-down >40° | SRc(-) 10.0 to 12.0mm | |
| *Bilateral inferior rectus recessions may cause A-pattern deviation because of weakened adduction in down gaze. The inferior rectus may be transposed nasally to avoid creating an A pattern. | | |
| Torsional AHP | Ipsilateral eye to tilt | Contralateral eye to tilt |
| Torsion 15° or less | Induce excyclotorsion Infraplacement of MR & Supraplacement of LR ½ TW | Induce incyclotorsion Infraplacement of LR & Supraplacement of MR ½ TW |
| Torsion 15° or greater | Induce excyclotorsion Infraplacement of MR & Supraplacement of LR 1 TW | Induce incyclotorsion Infraplacement of LR & Supraplacement of MR 1 TW |

| PAN(80-82) | Right Eye | Left Eye |
|---|--------------------------------|--------------------------------|
| | LRc(-) & MRc(-) 10.0 to 12.0mm | LRc(-) & MRc(-) 10.0 to 12.0mm |
| MRc(-) = medial rectus recession, LRc(-) = lateral rectus recession, MRs(+) = medial rectus resection; LRs(+) = lateral rectus resection, SRc(-) = superior rectus recession, IRc(-) = inferior rectus recession, BE = both eyes, TW = tendon width | | |

Table 6: Simplified guide to AHP surgery in INS

| Enquiries (phone, email and social media) to Nystagmus Network helpline 2015 | Number |
|---|---------------|
| UK general public enquiries | 495 |
| Overseas enquiries | 127 |
| Enquiries from UK professionals | 271 |
| Administration, fundraising, volunteering | 293 |
| Total | 1186 |

| UK general public enquiries by category | Number |
|--|---------------|
| General support & information | 233 |
| Research & treatment | 70 |
| Education | 64 |
| Benefits & discrimination | 47 |
| Acquired nystagmus | 29 |
| Employment | 18 |
| Driving & transport | 18 |
| Other | 16 |
| Total | 495 |

Table 7: A single year of enquiries to the patient support charity, Nystagmus Network (NN), in 2015. Source: data prepared for NN annual report 2015 and presented at NN Annual General Meeting, Birmingham, 7th May 2016.

| Name | Region | Website |
|--|---------------|---|
| Albinism Fellowship | National | http://www.albinism.org.uk/ |
| Aniridia Network | National | https://aniridia.org.uk/ |
| CVI Society (Cerebral Visual Impairment) | National | https://cvisociety.org.uk/ |
| LOOK | National | http://www.look-uk.org/ |
| Nystagmus Network | National | https://nystagmusnetwork.org/ |
| RNIB | National | https://www.mib.org.uk/ |
| VICTA | National | https://www.victa.org.uk/ |

Table 8: Examples of national support groups. It is important to note that many local support groups are also an excellent source of information and support for children with nystagmus and their families.

Figure Legends

Figure 1: How to draw a pedigree diagram whilst taking a family history. This pedigree is consistent with X-linked inheritance with variable penetrance in females (typical in *FRMD7* gene related INS).

Figure 2: Algorithm for the diagnostic use of OCT in INS (Adapted from Potential of handheld optical coherence tomography to determine cause of INS in children by using foveal morphology. *Ophthalmology*; 2013 Dec;120(12):2714-24.)

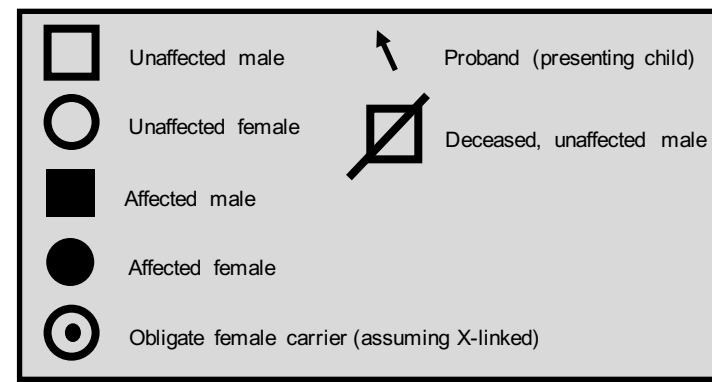
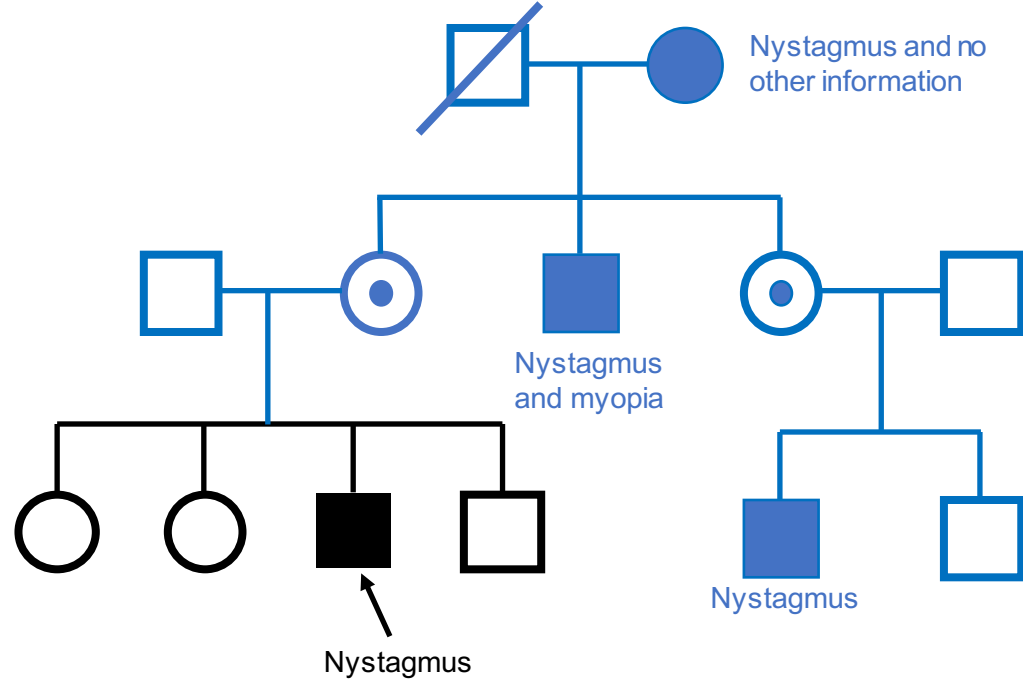
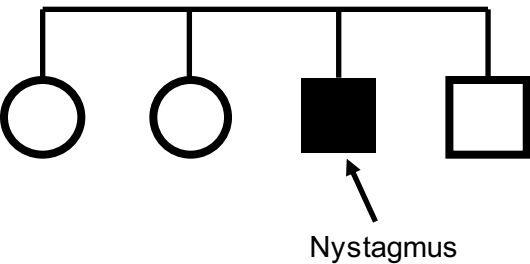
Figure 3: Foveal tomograms obtained from children, which demonstrate some of the diagnostic features seen in INS on OCT imaging. (Adapted from *Pediatric Optical Coherence Tomography in Clinical Practice-Recent Progress*)(17). (A) Typical foveal hypoplasia, where there is continuation of the normally absent IRLs (outlined in white) in a case of albinism. (B) Atypical foveal hypoplasia in achromatopsia where, in addition to foveal hypoplasia (IRLs outlined in white), there is Inner Segment Ellipsoid band (ISE) disruption and a hypo-reflective zone (white circle). (C) Normal foveal morphology. (D) Retinal dystrophy consisting of: absent rod photoreceptors and ISE (small white arrows), ONL thinning and abnormal lamination of the inner retinal layers seen in a case of microcephaly lymphoedema and chorioretinal dysplasia.

Figure 4: Algorithm for grading foveal hypoplasia on the basis of OCT findings. (Adapted from Structural grading of foveal hypoplasia using spectral-domain optical coherence tomography a predictor of VA)(34)

Figure 5: Examples of the use of eye tracking in clinical cases. (A) Schematic of idealised horizontal jerk nystagmus waveforms showing (top row) accelerating slow phases (ASP's) that are almost pathognomonic for infantile nystagmus (INS), and bottom row decelerating slow phases (DSP's), which are typically seen in FMNS and acquired gaze evoked nystagmus. (B) Example from a 6 year old boy referred with apparent recent onset of gaze-evoked nystagmus. Urgent brain MRI was normal and there were no other neurological signs. EOM recording revealed a conjugate horizontal jerk nystagmus in lateral gaze with clear ASPs (top panel). In primary position, nystagmus was not evident clinically, but recordings showed a very fine nystagmus with frequent ASPs (bottom panel). Conclusion was INS since infancy that had been undetected due to broad null around primary position, and MRI was had not been necessary. (C) A 15-year old female presented with spasms of oscillopsia and blurred vision that were correlated with clinically visible flutter-like episodes. EOM recording showed sporadic bursts of back-to-back saccadic oscillations that were predominantly horizontal. Episodes were not post-saccadic oscillations, as typically seen in ocular flutter, but were associated with spontaneous convergence and conjugate depression. Upon questioning, patient demonstrated ability to generate voluntary nystagmus with convergence at will. Precautionary brain MRI and chest X-ray were normal. Conclusion was 'involuntary' voluntary nystagmus or 'eye movement tic's' (4).

Figure 6: *Diagram summarising the role of paediatric visual electrodiagnostic work-up in infants and children presenting with nystagmus, of note this goes beyond the initial diagnostic workflow*

Figure 7: A diagnostic workflow that forms the basis of our clinical practice across a number of specialist paediatric nystagmus services in the UK. It is important to note that most cases will require additional evaluation for visual prognosis and/or monitoring (e.g. electrodiagnostics in the case with optic nerve hypoplasia) and this pathway is meant as a guide to seeking an initial diagnosis only.



Infantile Nystagmus Syndrome

Foveal Hypoplasia

Yes

No

Typical

Atypical

**Abnormal
Morphology
(Category 3)**

**Normal
Morphology
(Category 4)**

(Category 1)

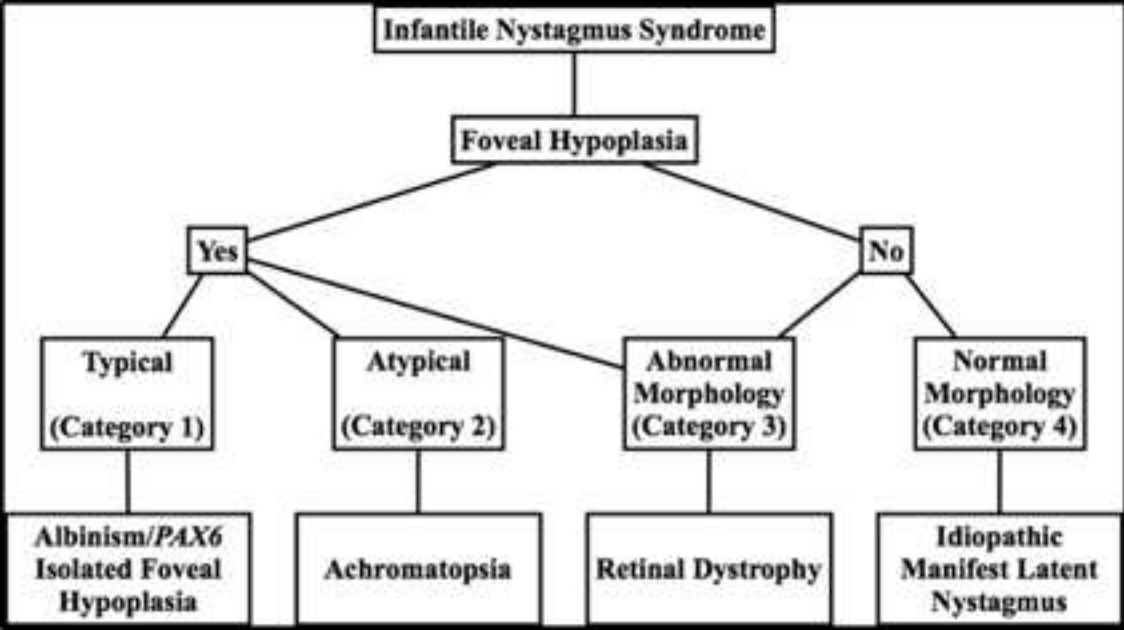
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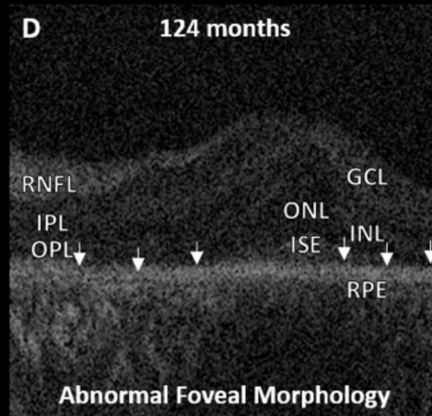
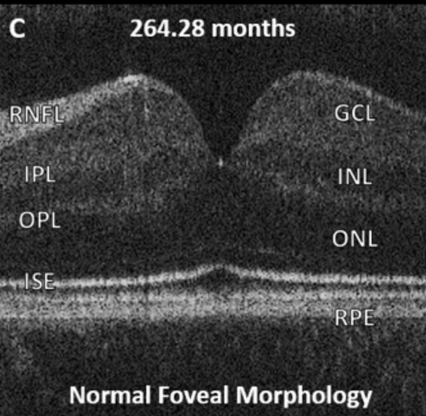
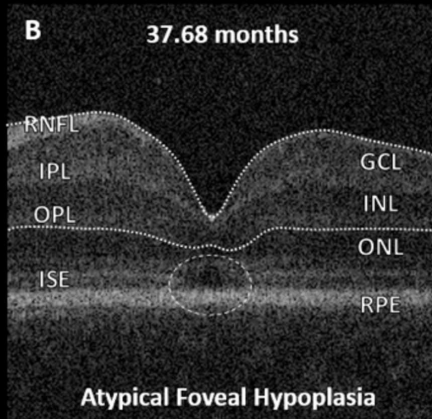
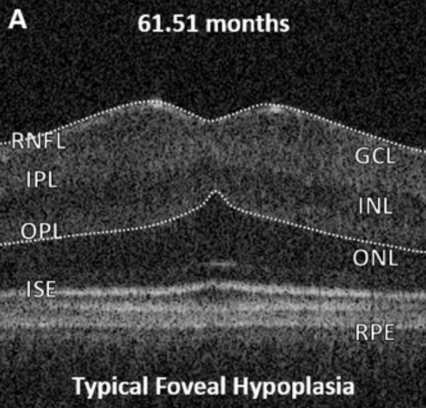
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Isolated Foveal
Hypoplasia**

Achromatopsia

Retinal Dystrophy

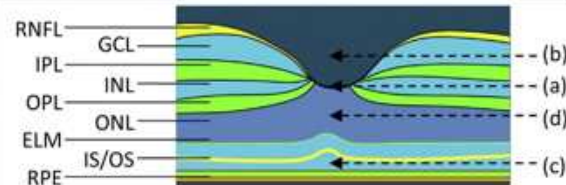
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Manifest Latent
Nystagmus**

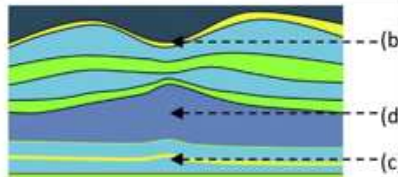
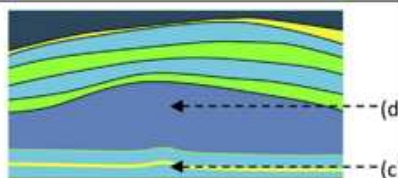
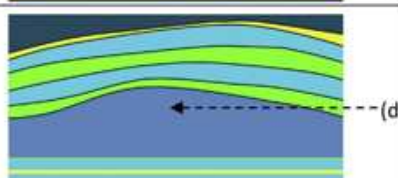

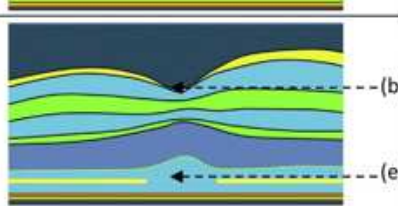


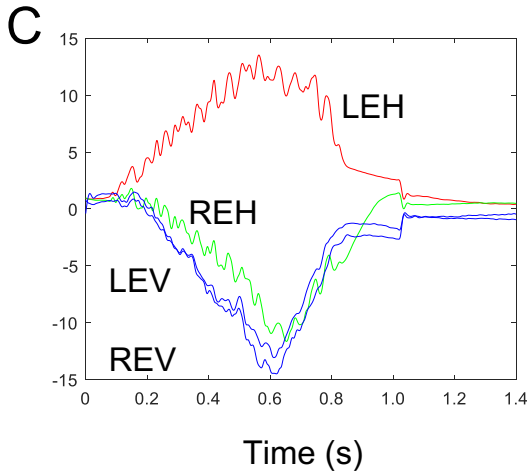
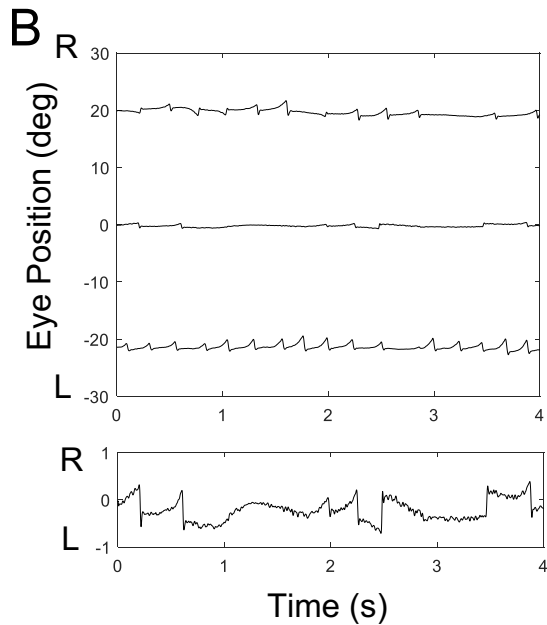
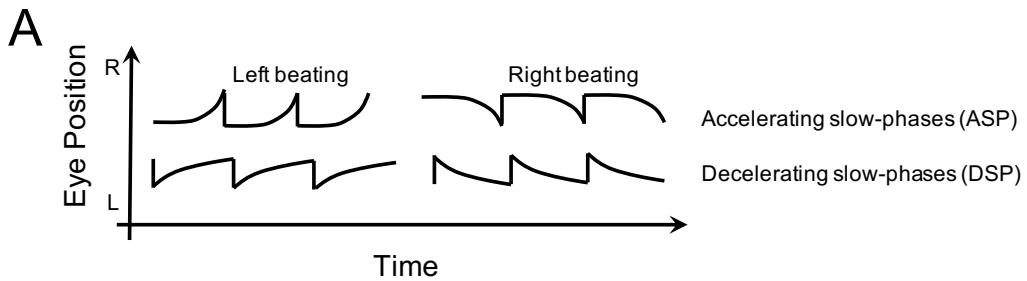


100 μm

1000 μm

| (A) Normal foveal structural features detectable using optical coherence tomography | Illustration |
|---|---|
| (a) Extrusion of plexiform layers (b) Foveal pit (c) OS lengthening (d) ONL widening |  <p>Diagram illustrating the normal foveal structure. The layers shown are: RNFL, GCL, IPL, INL, OPL, ONL, ELM, IS/OS, and RPE. The features (a) through (d) are indicated by dashed arrows pointing to the corresponding layers: (a) points to the ONL, (b) points to the foveal pit, (c) points to the IS/OS, and (d) points to the ONL.</p> |

| (B) Grade of foveal hypoplasia | Structural features detected on optical coherence tomography | Present or absent | Illustration |
|--------------------------------|---|---|---|
| 1 | (a) Extrusion of plexiform layers (b) Foveal pit – Shallow (c) OS lengthening (d) ONL widening | (a) Absent (b) Present (c) Present (d) Present |  <p>Diagram illustrating Grade 1 foveal hypoplasia. The features (a) through (d) are indicated by dashed arrows pointing to the corresponding layers: (a) points to the ONL, (b) points to the foveal pit, (c) points to the IS/OS, and (d) points to the ONL.</p> |
| 2 | (a) Extrusion of plexiform layers (b) Foveal pit (c) OS lengthening (d) ONL widening | (a) Absent (b) Absent (c) Present (d) Present |  <p>Diagram illustrating Grade 2 foveal hypoplasia. The features (a) through (d) are indicated by dashed arrows pointing to the corresponding layers: (a) points to the ONL, (b) points to the foveal pit, (c) points to the IS/OS, and (d) points to the ONL.</p> |
| 3 | (a) Extrusion of plexiform layers (b) Foveal pit (c) OS lengthening (d) ONL widening | (a) Absent (b) Absent (c) Absent (d) Present |  <p>Diagram illustrating Grade 3 foveal hypoplasia. The features (a) through (d) are indicated by dashed arrows pointing to the corresponding layers: (a) points to the ONL, (b) points to the foveal pit, (c) points to the IS/OS, and (d) points to the ONL.</p> |
| 4 | (a) Extrusion of plexiform layers (b) Foveal pit (c) OS lengthening (d) ONL widening | (a) Absent (b) Absent (c) Absent (d) Absent |  <p>Diagram illustrating Grade 4 foveal hypoplasia. The features (a) through (d) are indicated by dashed arrows pointing to the corresponding layers: (a) points to the ONL, (b) points to the foveal pit, (c) points to the IS/OS, and (d) points to the ONL.</p> |
| Atypical | (a) Extrusion of plexiform layers (b) Foveal pit – Shallow (e) IS/OS disruption | (a) Absent (b) Present (e) Present |  <p>Diagram illustrating Atypical foveal hypoplasia. The features (a) through (e) are indicated by dashed arrows pointing to the corresponding layers: (a) points to the ONL, (b) points to the foveal pit, (c) points to the IS/OS, and (d) points to the ONL.</p> |



Electrodiagnostics in infants & children presenting with nystagmus

Flash ERGs

Mixed cone/rod

Cone ERGs

Rod ERGs

Photoreceptor dysfunction e.g.:

Rod-cone dystrophies, Cone-rod dystrophies,
achromatopsia, blue-cone monochromatism,
Leber's amaurosis

Inner retinal dysfunction (electronegative ERG):

CSNB

Retinoschisis

Pattern and Flash VEPs

Binocular VEP

Monocular VEP

Post-retinal dysfunction
e.g.:

Optic nerve hypoplasia,
Cortical visual impairment

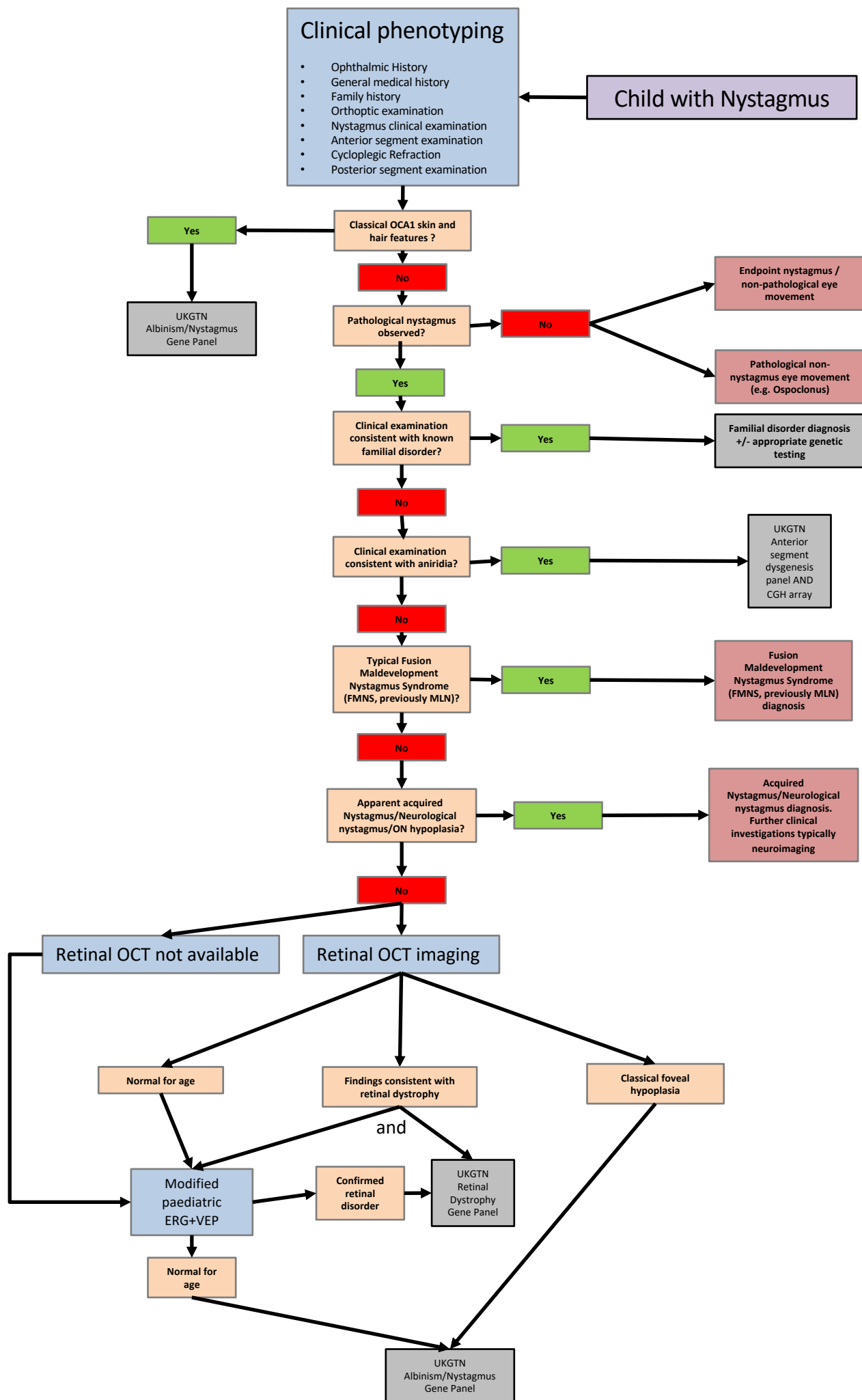
Estimation of visual
potential

Crossed occipital
asymmetry e.g.:

Albinism
Achromia
Chiasmal
compression

Uncrossed
occipital
asymmetry e.g.:

Retro-chiasmal /
unilateral
hemisphere lesions



Management of nystagmus in children: a review of the literature and current practice in UK specialist services

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Abstract

Nystagmus is an eye movement disorder characterised by abnormal, involuntary rhythmic oscillations of one or both eyes, initiated by a slow phase. It is not uncommon in the UK and regularly seen in paediatric ophthalmology and adult general/strabismus clinics. In some cases, it occurs in isolation, and in others, it occurs as part of a multisystem disorder, severe visual impairment or neurological disorder. Similarly, in some cases, visual acuity can be normal and in others can be severely degraded. Furthermore, the impact on vision goes well beyond static acuity alone, is rarely measured and may vary on a minute-to-minute, day-to-day or month-to-month basis. For these reasons, management of children with nystagmus in the UK is varied, and patients report hugely different experiences and investigations. In this review, we hope to shine a light on the current management of children with nystagmus across five specialist centres in the UK in order to present, for the first time, a consensus on investigation and clinical management.

儿童眼球震颤的管理：英国专家服务的文献回顾与现行指南

摘要：

眼球震颤是一种眼球运动障碍以单眼或双眼异常的、不自主的节律性摆动为特征，其发病缓慢。在英国的发病率不低，通常就诊于小儿眼科和成人普通/斜视门诊。眼球震颤在某些情况下单发，也可伴发多系统疾病、严重视力损害或神经系统疾病。同样，在一些病例中，患者视力正常，另一些病例中，患者视力严重下降。而且其对视力的影响远超过对静态视敏度的影响，几乎检测不到，而且可能在每分钟、每天或每月的基础上不断变化。基于以上原因，在英国，针对儿童眼球震颤的管理是多样的，而且患者的症状与调查报告也有很大的差别。我们希望本文能从英国五个专科中心的眼球震颤儿童的现行的管理有所启发，以便首次达成调查与临床管理共识。

20799;31461;30524;29699;38663;39076;30340;31649;29702;
65306;33521;22269;19987;23478;26381;21153;30340;25991;
29486;22238;39038;19982;29616;34892;25351;21335;

25688;35201;65306;

30524;29699;38663;39076;26159;19968;31181;30524;29699;
36816;21160;38556;30861;20197;21333;30524;25110;21452;
30524;24322;24120;30340;12289;19981;33258;20027;30340;
33410;24459;24615;25670;21160;20026;29305;24449;65292;
20854;21457;30149;32531;24930;12290;22312;33521;22269;

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就诊于小儿眼科和成
人普通/斜视门诊。
0524;球震颤在某些情况
9979;单发，也可伴发多
1995;统疾病、严重视力
5439;害或神经系统疾病
2290;同样，在一些病例
0013;，患者视力正常，
1478;一些病例中，患者
5270;力严重下降。而且
0854;对视力的影响远超
6807;对静态视敏度的影
1709;，几乎检测不到，
2780;且可能在每分钟、
7599;天或每月的基础上
9981;断变化。基于以上
1407;因，在英国，针对
0799;童眼球震颤的管理
6159;多样的，而且患者
0340;症状与调查报告也
6377;很大的差别。我们
4076;望本文能从英国五
0010;专科中心的眼球震
9076;儿童的现行的管理
6377;所启发，以便首次

6798;#25104;#35843;#26597;#19982;#20020;#24202;#31649;#29702;#2
0849;#35782;#12290;